REMARKS

Claims 14-21 are all the claims pending in the application; each of the claims has been rejected.

Claims 14-17 have been amended as previously proposed by the Examiner (in the telephone conference with the undersigned on December 9, 2002). Support for the amendment may be found in the specification at, for example, page 7, lines 4-21; page 10, lines 4-8; page 11, line 25 through page 12, line 3; and page 14, lines 3-5.

No new matter has been added. Entry of the amendment is respectfully requested.

I. Rejection of Claims 14-21 under 35 U.S.C. § 103

Claims 14-21 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,990,503 to Isomura *et al.* in view of Aparicio *et al.* (Leukemia 12:220-229 (1998)) and Shipman *et al.* (Br. J. Haematology 98:665-672 (1997)).

The Examiner repeats the reasons for the rejection stated in the non-final Office Action dated December 18, 2003.

In response, Applicants include herewith amendments to the claims where claims 18-21 are canceled, and claims 14-17 have been amended in the manner suggested by the Examiner. During a telephone call with the undersigned on December 9, 2002, the Examiner stated that the claims would be in condition for allowance if they were amended to recite a method of treating multiple myeloma. None of the art cited by the Examiner teaches the use of the bisphosphonate (BP) compound of the present invention in the treatment of multiple myeloma.

Applicants also note that in the outstanding Office Action, the Examiner identified the dosage of a bisphosphonate administered to a mouse as 4 ug (the Dallas article) and that because

a higher dosage is recited in the claims of the instant application, *in vivo* effects would be expected. However, as discussed in the paragraph titled "Ibandronate Administration" in the right column of page 1698 of Dallas, the dose of 4 ug (0.16 mg/kg) of ibandronate was at "the highest end of the range of doses tested in various animal models of normal and pathologic bone resorption." It is also described that this dose is approximately 100-fold higher than the optimum dose as an bone resorption inhibition (third full paragraph, column 2, page 1698). Even in such a case, the blood concentration of the drug is about $1/10^{th}$ of the concentration that exhibits *in vitro* inhibition of multiple myeloma cell (MM) proliferation (first full paragraph, column 2, page 1705). Thus, it is concluded in Dallas that the *in vivo* induction of MM cell apoptosis cannot be expected. Accordingly, one skilled in the art would have considered from this article that it would be difficult to achieve an *in vivo* drug concentration that exhibits MM proliferation inhibiting activity at the clinical dose for the bone resorption inhibiting agent.

The Examiner also found that the present invention is "reasonably expected to be effective" by alleging that various BPs are known to be effective in both inducing apoptosis in MM cells and inhibiting bone resorption. However, these effects are the results of the tests which were carried out under different concentrations and conditions, and thus the results do not suggest the possibility of exhibiting both the effects at the same time. In fact, with respect to the BPs reported, there is no evidence shown for the achievement of an *in vivo* concentration as high as the concentration required for inducing apoptosis *in vitro*, when the particular BP reported was administered in a dose for exhibiting bone resorption inhibiting activity. Because Dallas clearly denies the possibility, Applicants respectfully state that the Examiner's finding of "reasonably expected to be effective" is incorrect.

As explained above, even assuming that Isomura et al. (which allegedly discloses the bone resorption inhibiting activity of Compound A) could be combined with Aparicio et al. and Shipman et al. (which disclose *in vitro* MM cell proliferation inhibiting activity of other BPs), the combination does not teach or suggest the method of treating MM by inhibiting proliferation of myeloma cells and suppressing bone resorption when Compound A is administered to multiple myeloma patients having bone lesions. Thus, the present invention is unobvious.

In view of the points discussed above, and the amendment to the claims, Applicants assert that the pending claims are not obvious over the literature cited by the Examiner, and therefore respectfully request reconsideration and withdrawal of this rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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